Enantioselective Rhodium-Catalyzed Addition of Potassium Alkenyltrifluoroborates to Cyclic Imines**

Yunfei Luo, Andrew J. Carnell, and Hon Wai Lam*

Chiral α-branched allylic amines are important building blocks for organic synthesis, and several catalytic asymmetric methods have been developed for their synthesis. For example, enantioselective metal-catalyzed amination of allylic electrophiles[1,2,3] and rearrangement of allylic imidates[4,5,6] have proven to be highly effective.

An alternative approach to chiral allylic amines that can be advantageous from the viewpoint of convergency is the catalytic enantioselective union of an alkynyl nucleophile with an imine.[7,8,9,10,11,12] In view of the widespread success of enantioselective Rh(I)-catalyzed additions of arylboron reagents to imines as a means to access chiral α-aryl branched amines,[13,14,15] development of the corresponding reactions of alkenylboron reagents to prepare chiral α-branched allylic amines should be an attractive goal. Surprisingly however, only very limited precedent exists for this transformation.[16]

Brak and Ellman have developed highly diastereoselective Rh(I)-catalyzed additions of alkenylboron reagents to imines (Scheme 1A).[17] The only existing enantioselective variant is that of Shintani, Hayashi, and co-workers who, as part of a study involving additions of potassium aryll trifluoroborates to N-sulfonyl ketimines, also described one example using an alkenyltrifluoroborate (Scheme 1B). [15c] Also of relevance is a single example of an enantioselective Rh(I)-catalyzed addition of an alkenylsilane derived from chiral diene ligands[21,22] (Table 1).

Given that imines 1a–1d are highly effective substrates for enantioselective Rh(I)-catalyzed additions of arylboron reagents,[14] and chiral diene L1 has provided excellent results in these types of reactions,[15c] we were surprised to learn that imine alkenylation was far from straightforward. This study began with attempted alkenylation of acyclic imines 1a–1d with potassium (E)-1-hexenyltrifluoroborate (2 equiv) at 80 °C in dioxane for 24 h in the presence of MeOH (5 equiv) and 1.5 mol% of the dimeric rhodium complexes derived from chiral diene ligands[21,22] L1,[15a] or L2[23] (Table 1). Given that imines 1a–1d are highly effective substrates for enantioselective Rh(I)-catalyzed additions of arylboron reagents, L1 has provided excellent results in these types of reactions,[15c] we were surprised to learn that imine alkenylation was far from straightforward.

Herein, we demonstrate that cyclic imines are highly effective substrates for enantioselective Rh(I)-catalyzed additions of potassium alkenyltrifluoroborates,[19,20] providing products in excellent enantioselectivities and generally good yields. The cyclic structure of these imines, where the C=C=N bond is constrained in the Z-geometry, appears to be important for the success of the reactions.

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** Significance of chiral allylic amines;
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[**] We thank the ERC (Starting Grant No. 258580) and the EPSRC (Leadership Fellowship to H. W. L) for support of this work. Dr. Gary S. Nichol (University of Edinburgh) for X-ray crystallography, and the EPSRC National Mass Spectrometry Service Centre at the University of Wales, Swansea, for high resolution mass spectra.

Supporting information for this article is available on the WWW under http://www.angewandte.org

Table 1: Attempted Rh-catalyzed alkenylation of various imines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Ligand</th>
<th>Product</th>
<th>Yield [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>L1</td>
<td>3a</td>
<td>&lt;5</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>L1</td>
<td>3b</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>L1</td>
<td>3c</td>
<td>&lt;5</td>
<td>n/a</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>L1</td>
<td>3d</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>2a</td>
<td>L1</td>
<td>4a</td>
<td>76</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>2a</td>
<td>L2</td>
<td>4a</td>
<td>&gt;95</td>
<td>98</td>
</tr>
</tbody>
</table>

[a] NMR yields calculated using nitromethane as an internal standard.
[b] Determined by HPLC analysis on a chiral stationary phase. [c] Significant decomposition of 1c was observed.
Tosylimine 1a and diphenylphosphinoylimine 1c were not viable substrates, and no alkenylation was observed using L1 (entries 1 and 5). In these reactions, imine 1a remained largely intact, but imine 1c underwent significant decomposition. While appreciable alkenylation was observed using L1 with both nosylimine 1b and N,N-dimethylsulfamylimine 1d, the enantiomeric excesses of the corresponding products were low (entries 3 and 7). Similar results were obtained using L2 as the ligand (entries 2, 4, 6, and 8), with the exception that alkenylation was significant with nosylimine 1b (entry 4).

The results of entries 1–8 clearly highlight the difficulties of these alkenylation reactions compared with the corresponding arylations. The mostly poor conversions into the desired products may be explained by the lower stability of alkenylrhodium species compared with arylrhodium species, which renders protodeboronation or decomposition pathways highly competitive with imine addition. However, it is more difficult to rationalize the low enantioselectivities obtained when alkenylation was successful (Table 1, entries 3, 4, 7, and 8). One factor to consider in all catalytic asymmetric additions to imines is the possibility of E/Z isomerization of the imine during the reaction, which usually has a negative impact upon stereoselectivity. Although this issue does not appear to be problematic for Rh(I)-catalyzed imine arylation, we surmised that it could be important in imine alkenylation.

To test this theory, the alkenylation of benzoxathiazine-2,2-dioxide 2a, a cyclic imine where E/Z isomerization is precluded, was examined. Surprisingly, to our knowledge, benzoxathiazine-2,2-dioxides have been virtually unexplored as electrophiles for carbon nucleophiles. We were therefore delighted to observe that under conditions identical to those employed for imines 1a–1d, imine 2a provided the alkenylation product 4a in high conversions and enantioselectivities (Table 1, entries 9 and 10), with ligand L2 giving the best results (entry 10).

Under the optimized conditions, imine 2a smoothly reacted with various alkenyltrifluoroborates containing alkyl (Table 2, entries 1, 3, and 4) or aryl (entry 5) substituents at the β-carbon to provide alkenylation products in good yields and high enantioselectivities (95–99% ee). In addition, vinylation was successful (entry 2), and substitution at the α-carbon of the alkenyltrifluoroborate was tolerated (entry 6). Interestingly, conducting the experiments in entries 2 and 3 with the corresponding alkyn MIDA boronates in place of the alkenyltrifluoroborates under conditions described by Brak and Ellman provided only <20% conversion into 4b and 4c, respectively.

Table 3 presents the alkenylation of more highly substituted benzoxathiazine-2,2-dioxides. Imines containing a range of arene substituents (including methyl, methoxy, chloro, bromo, and fluoro) at various positions were competent substrates, providing alkenylation products in >81% yield and ≥94% ee (products 5a–5i). However, the reaction of potassium vinyltrifluoroborate with a benzoxathiazine-2,2-dioxide containing the electron-donating dioxole group provided 5j in only 50% yield, though in 97% ee. Presumably, the modest yield observed here is due to the greater propensity of potassium vinyltrifluoroborate to undergo protodeboronation compared with its more sterically

Table 3: Alkenylation of various benzoxathiazine-2,2-dioxides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Trifluoroborate</th>
<th>Product</th>
<th>Yield [%][a]</th>
<th>ee [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KF3BF3Bu</td>
<td>4a</td>
<td>90</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>KF3BF3Me</td>
<td>4b</td>
<td>75</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>KF3BF3Cy</td>
<td>4c</td>
<td>79</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>KF3BF3PMP</td>
<td>4d</td>
<td>94</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>KF3BF3Me</td>
<td>4e</td>
<td>88</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>KF3BF3Cy</td>
<td>4f</td>
<td>94</td>
<td>94</td>
</tr>
</tbody>
</table>

[a] Isolated yields. [b] Determined by HPLC analysis on a chiral stationary phase. PMP = para-methoxyphenyl.
hindered counterparts, a problem that is compounded by the lower electrophilicity of this imine. As expected, a more highly substituted alkenyltrifluoroborate provided better results, with 5k being formed in 93% yield and 94% ee. Finally, the benzothiazine-2,2-dioxide derived from 2-hydroxy-1-naphthaldehyde was also a suitable substrate, though the steric hindrance associated with this imine led to the product 5l being formed in a modest 55% yield.

Cyclic N-sulfonyl ketimine 6 was also a viable substrate, providing sultam 7 in 68% and 90% ee [Eq. (1)]. This result further confirms the beneficial effect of a cyclic imine structure, and demonstrates that the high efficiency of these reactions is not confined to benzothiazine-2,2-dioxides.

Scheme 2 illustrates the utility of the alkenylation products. Aryl sulfamates have recently been shown to be highly effective in a range of nickel-catalyzed cross-coupling reactions. For example, Wehn and Du Bois have described Kumada couplings of cyclic aryl sulfamates, and Garg and co-workers have developed Suzuki–Miyaura reactions of their acyclic counterparts. It was therefore of interest to ascertain whether nickel-catalyzed Suzuki–Miyaura reactions would be successful with cyclic aryl sulfamates derived from the alkenylation products of this study. To this end, 4a was converted into cyclic sulfamate 8 by alken hydrogenation followed by N-methylation. Gratifyingly, application of Garg’s conditions for Suzuki–Miyaura coupling of 8 with PhB(OH)2 smoothly delivered the biaryl compound 9 in 72% yield after amidated cleavage of the sulfamic acid intermediate.

Next, a hydroboration/oxidation sequence of 4b gave alcohol 10 in 91% yield. Treatment of 8 with LiAlH4 at reflux followed by Boc2O provided carbamate 11, which was then converted into chroman-4-amide 12 via a Mitsunobu cyclization. Chroman-4-amines appear as core scaffolds in several drug discovery programs, for example in the human bradykinin B1 receptor antagonist 13.

Finally, N-allylation of 4b gave diene 14 which underwent efficient ring-closing metathesis using the 2nd generation Grubbs catalyst to give dihydropyrrole 15. Dihydroxylation of 15 from the least hindered face followed by acetamide protection of the resulting diol provided 16, which was then transformed into the biaryl-containing dihydroxylated pyrroldine 17 in 84% yield by nickel-catalyzed Kumada coupling with PhMgBr and acidic workup according to the method of Wehn and Du Bois. 2-Aryl dihydroxylated pyrrolidines similar to 17 are of interest as potential glycosidase inhibitors.

In conclusion, the first enantioselective Rh-catalyzed additions of alkenylboron compounds to cyclic imines have been described. The cyclic structure of these imines, where the C=N bond is constrained in the Z-geometry, appears to be important, allowing alkenylation to proceed in generally good

The sense of enantiomdentation of these reactions is consistent with the stereochemical model proposed for the 1,4-arylation of cyclic enones. Following this model, binding of the imine to the chiral diene-ligated alkenylrhodium species is suggested to occur in a manner that minimizes unfavorable nonbonding interactions between the imine activating group and one phenyl substituent of the ligand (Figure 1). Carboration from the re-face of the imine then occurs to eventually provide the product.

\[ \text{Disfavored} \quad \text{Favored} \]

\[ \text{Figure 1. Possible stereochemical model for the formation of 4.} \]

\[ \begin{align*}
\text{4a (98% ee)} & \quad \text{1. H}_2, \text{Pd/C} \quad \text{EtOH} \quad \text{RT} \\
& \quad \text{2. K}_2\text{CO}_3, \text{MeCN} \quad \text{RT} \\
& \quad \text{95%}
\end{align*} \]

\[ \begin{align*}
\text{4b (98% ee)} & \quad \text{9-BBN, THF} \quad 0 \degree \text{C} \quad \text{to RT} \\
& \quad \text{then NaOH, } \text{H}_2\text{O} \quad 91% \\
& \quad \text{allyl bromide, } \text{K}_2\text{CO}_3, \text{MeCN} \quad \text{RT} \\
& \quad \text{95%}
\end{align*} \]

\[ \begin{align*}
\text{14} & \quad \text{Grubbs II (3 mol%)} \quad \text{CH}_2\text{Cl}_2 \quad 95% \\
\text{15 (98% ee)} & \quad \text{1. OsO}_4, \text{NMO} \quad \text{THF} \quad \text{RT} \\
& \quad \text{2. } \text{Me}_2\text{C}=(\text{OMe})_2, \text{TsOH} \quad \text{RT} \\
& \quad \text{95%}
\end{align*} \]

\[ \begin{align*}
\text{16} & \quad \text{1. NiCl}_2(\text{PCy}_3)_2(20 \text{ mol%}) \quad \text{toluene, } \Delta \\
& \quad \text{then HCl, MeOH, 50 °C} \\
\text{9 (98% ee)} & \quad \text{72%}
\end{align*} \]

\[ \begin{align*}
\text{17} & \quad \text{13 (bradykinin B1 receptor antagonist)}
\end{align*} \]
yields and high enantioselectivities (≥94% ee). Moreover, products containing aryl sulfamates may be exploited in subsequent reactions, including nickel-catalyzed cross-couplings, to generate further useful compounds.


For another application of these cyclic N-sulfonyl ketimines in catalysis, see: M. Rommel, T. Fukuzumi, J. W. Bode, *J. Am. Chem. Soc.* **2008**, *130*, 17266-17267.


For a proposed catalytic cycle for these reactions, see Supporting Information.


Enantioselective Rhodium-Catalyzed Addition of Potassium Alkenyltrifluoroborates to Cyclic Imines

**Fixed:** Cyclic imines, where the C=N bond is constrained in the Z-geometry, have been identified as highly effective substrates for enantioselective rhodium-catalyzed additions of potassium alkenyltrifluoroborates. Not only is the alkene in the products a useful functional handle for subsequent manipulations, products containing aryl sulfamates may be employed in nickel-catalyzed Suzuki-Miyaura and Kumada couplings to generate further compounds of interest.